REMARKS

Claims 11,14, 15, 17, 19, and 20 currently appear in this application. The Office Action of November 23, 2001, has been carefully studied. It is believed that all of the claims are allowable, and favorable action is earnestly requested.

Rejections under 35 U.S.C. 112

Claims 1-3 and 11-13 are rejected under 35 U.S.C. 112, first paragraph, because the specification is said not to provide enablement for vitamin D compounds other than those disclosed in the specification at page 4, lines 6-21.

This rejection is respectfully traversed. The claims have now been amended to recite the specific vitamin D compounds disclosed in the specification at page 4, lines 12-19.

Claims 1-3, 5-13 and 15-20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

This rejection is respectfully traversed. The claims have now been amended to recite specific vitamin D compounds.

Art Rejections

Claims 1-20 are rejected under 35 U.S.C. 102(b) as being anticipated by Itoh et al. The Examiner alleges that Itoh et al. teach an ophthalmic composition comprising calcitrol.

This rejection is respectfully traversed. Itoh et al. state that the ophthalmic composition is designed for preventing deterioration after operation of the ocular optical transparency due to hyperplasia of anterial ocular cells in the tissues damaged by an ophthalmic operation (column 3, line 61 through column 5, line 2). There is nothing at all in Itoh et al. that discloses or suggests using the compounds of the present invention to inhibit ocular Langerhans cell migration. To establish inherency, the extrinsic evidence must "make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be recognized by persons of ordinary skill." *Continental Can Co. v. Monsanto co.*, 20 USPQ (Fed. Cir. 1991).

Additionally, the discovery of a new use for a compound is patentable. The present inventors have discovered a new use of the herein claimed vitamin D compounds, namely, inhibiting ocular Langerhans cell migration. As disclosed in the specification at page 1, lines 18-25, Langerhans cells are deeply involved in the development stage of immunoreactive inflammation of the skin and cornea, and continued limitation of the number of these cells at the entry site of foreign antigens seems to prevent inflammation at the surrounding sites. Unlike conventionally used medications for inhibiting immunoreaction in the skin or cornea, the compounds of the present invention can be used **prior** to the occurrence of

inflammation. Itoh et al., on the other hand, disclose a composition for controlling hyperplasia, an increase in the number of cells in a tissue, rather than preventing migration of specific cells into the cornea or skin.

Claims 1-20 are rejected under 35 U.S.C. 102(e) as being anticipated by Itoh et al. '709.

This rejection is respectfully traversed. For the reasons given above, there is nothing inherent in the Itoh et al. disclosure that addresses preventing migration of Langerhans cells to an area.

Claims 11-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dam et al. in view of Itoh et al., Hingorani et al., and Muller et al.

This rejection is respectfully traversed. Dam et al. merely describe that a short-term application of calcipotriol cream to normal skin resulted in a dose-dependent decrease in the number of Langerhans cells. In this connection, Dam et al. further describe, on page 76, left column, lines 10-6 from the bottom, that, taken together with the inhibition of monocyte TNF-α production by vitamin D_3, it is possible that calcipotriol might modify epidermal Langerhans cell migration by changing the epidermal concentrations of TNF-α.

Thus, Dam et al. indicate that the dose-dependent decrease in the number of Langerhans cells is due to the inhibition of monocyte TNF-α production by calcipotriol. That is, Dam et al. suggest that calcipotriol acts on

monocytes to inhibit their production of TNF-α, and the inhibition, in turn, decreases the number of Langerhans cells migrating. This means that the presence of monocytes in an amount sufficient to affect the migration of Langerhans cells is essential for inhibiting this migration.

However, since it has been unknown that monocytes are present in **eyes** in such as amount, one of ordinary skill in the art would not expect that calcipotriol inhibits Langerhans cell migration in the eyes.

In contrast thereto, the present invention is based upon the discovery that the inhibition of Langerhans cell migration in the corneal epithelium by 1α, 25 dihydroxy vitamin D_3 results from inhibition of IL-1 production in the corneal epithelium by 1α, 25 dihydroxy vitamin D_3. This is clearly disclosed in the present specification at page 12 lines 10-14.

Thus, the mechanism of Dam et al. differs from that of the present invention in inhibiting Langerhans cell migration. This is because Dam et al. treat normal skin, and the present invention is directed to treating eyes, which are not considered to be normal skin.

Itoh et al., Hingorani et al., and Muller et al. are silent with respect to inhibiting migration of Langerhans cells in the eye. In fact, Muller et al. only disclose that 1,25-D_3 reduces the levels of IL-1α mRNA.

Thus, there is no motivation for one skilled in the art from the combination of Dam et al., Itoh et al.,

Hingorani et al, and Muller et al. to inhibit Langerhans cell migration in an eye using the specific vitamin D derivatives of claim 11.

In view of the above, it is respectfully submitted that the claims are now in condition for allowance, and favorable action thereon is earnestly solicited.

Respectfully submitted,
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IN THE SPECIFICATION

Page 1, please amend the last paragraph lines 26-28 through page 2 lines 1-4 as follows:

At present, potent drugs such as steroids and ~~cyclospoliin~~ cyclosporin A are used to inhibit immunoreaction in the skin or cornea, but these drugs are inappropriate for use before inflammation occurs because of their various side effects. Therefore, there is a demand for development of a drug with less side effects that can be safely used before inflammation occurs.

Page 4, please amend the last paragraph lines 22-28 through page 5 lines 1-20 as follows:

The Langerhans cell migration inhibitor of the present invention is generally used in the form of a pharmaceutical composition comprising active vitamin D in combination with a pharmaceutical carrier and formulated as a solution or ointment for topical administration. The compositions are preferably formulated as an opthalmic liniment, especially an opthalmic solution. Examples of carriers suitable for these formulations include, but **are** not limited to, water, ethanol, ethylene glycol, propylene glycol, polyvinyl alcohol, polyvinyl pyrrolidone, gum arabic, calcium phosphate, alginate, gum

tragacanth, gelatin, methylcellulose, talc, magnesium stearate, hyaluronic acid, chondroitin sulfate, collagen, fat and mineral oils. In addition to these carriers, the pharmaceutical compositions of the present invention may contain other additives such as a stabilizer, preservative, isotonizing agent, pH-modifier, antioxidant and colorant. Examples of the stabilizer include, but **are** not limited to, sodium bisulfite, glycerin, sodium edetate, sodium citrate and butyl hydroxyanisole. Example of the preservative include, but **are** not limited to, benzalkonium chloride. Example of the isotonizing agent include, but **are** not limited to, sodium chloride, D-mannitol, glucose and glycerin. Example of the pH-modifier include, but **are** not limited to, phosphates such as monosodium phosphate and sodium hydrogenphosphate, sodium hydroxide and hydrochloric acid. Examples of the antioxidant include, but **are** not limited to, vitamin C.

IN THE CLAIMS

11. (Amended) A method for ~~prevention and/or treatment of skin or ocular inflammation~~**inhibitory ocular Langerhans cell migration** in a mammal comprising administering an effective amount of a ~~langerhans~~ **Langerhans** cell migration inhibitor comprising ~~active vitamin D~~**a compound selected from dihydroxy vitamin D_3; α-**

calcidol; calcifedol; 1α, 25,26-trihydroxy vitamin D_3; 1β,25-dihydroxy vitamin D_3; 24-homo-1α,25-dihydroxy vitamin D_3; 22-oxacalcitol; and calcipotriol as an active ingredient to the mammal.

14. (Amended) The method of Claim ~~13~~ 11 wherein the ~~active vitamin D_3~~ compound is calcitriol or 22-oxacalcitriol.

17. (Amended) The method of Claim ~~16~~ 15 wherein the ~~ocular inflammation is~~Langerhans cell migration causes keratoconjunctivitis.

19. (Amended) The method of Claim ~~18~~ 15 wherein the ~~ocular inflammation is~~Langerhans cell migration causes phlyctenular keratitis or corneal infiltration.

20. (Amended) The method of Claim 15 wherein the inhibitor prevents and/or treats an ocular inflammation by inhibiting the production of interleukin-1 in corneal epithelial cells caused by Langerhans cell migration.